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David S. Harper
McDonnell Boehnen Hulbert & Berghoff LLP
Suite: 3100
300 South Wacker Drive
Chicago, IL 60606

EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,118	CROWLEY ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2010 and 23 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/07, 7/23/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 10/20/10 to claims 1-9 and 1-15 have been entered. Claim 10 has been canceled. Claims 1-9 and 11-15 remain pending in the current application.

The examiner notes that applicant has referred to various paragraphs of the specification. Reply at 5. Applicant is reminded that the specification under consideration is the one submitted on 8/30/06, NOT the published application. The examiner is considering the original specification only. To expedite examination, applicant should refer to pages and line numbers from that document, NOT paragraphs from the published application. Applicant's cooperation is appreciated.

Election/Restrictions

In an interview on 7/22/10, the examiner indicated that applicants were free to amend claims 10 and 14 to recite species not contained in the original claim listing, so long as applicants made a species election that was commensurate in scope with the amendments. Applicants canceled claim 10, obviating the current requirement for an election of cells. Applicants amended claim 14 to recite only two species, "a protein" and "a polynucleotide."

Applicant's election of the species "mammalian cells" and "a polypeptide" in the reply filed on 7/23/10 (and reiterated in the 10/20/10 reply) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the

restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The examiner interprets applicants' election of "a polypeptide" as reading on the species "a protein" recited in claim 14. Although the claims do not currently recite a Markush group that includes non-mammalian cells (as canceled claim 10 did), applicants' election of "mammalian cells" will apply if such a claim is added to the listing later in prosecution.

Examination on the merits commences on claims 1-9 and 11-15, to the extent that claim 14 reads on the elected species.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-9 and 11-15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a method, but in one reasonable interpretation, they do not recite any active method steps. Claim 1 is drawn to "a method for reducing cell aggregation during continuous perfusion culturing" and goes on to recite numerous "wherein" clauses. In one reasonable interpretation of the claim, these "wherein" limitations are not active steps, but rather a description of the "continuous perfusion culturing" in the preamble that is improved by some unnamed method steps. This rejection would be overcome by an amendment to the claims that unequivocally recites active steps.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 does not clearly recite any method steps. It is not clear which steps are required for the method and which are not. The claim does not, for example, require an active step of adding medium to the cell culture or circulating the culture. The “wherein” limitations merely describe a culture method that might be modified to reduce cell aggregates by some unrecited steps. Clarification is required.

Claim 1 is drawn to a method for “reducing cell aggregation,” which is confusing because there is no point of reference provided for the relative term “reducing.” Clarification is required.

Furthermore, claim 1 includes the functional limitations “wherein no more than 5% of the animal cells in the culture form aggregates of at least 5 cells during the continuous perfusion culturing” and “resulting in an outflow of liquid having a lower animal cell density than the cell culture,” which is confusing because it is not clear whether these effect is an inherent result of some process steps (presumably, culture, addition of media, and/or circulation over a filter module) or whether some additional step is required to achieve this result. Clarification is required.

Claim 1 refers to "an outflow" at line 5, but it is not clear how this "outflow" relates to the remainder of the method. The claim does not refer to or suggest any particular apparatus. Clarification is required.

Claim 1 might be interpreted as being drawn to a three-step method in which the steps may be carried out sequentially or simultaneously:

(a) carrying out continuous perfusion culture of animal cells in culture medium;

(b) adding culture medium to the culture; and

(c) circulating the animal cells in culture medium over a filter module that comprises hollow fibers "in an alternating tangential flow,"

until the culture contains at least 80 x 10^6 cells per mL of medium.

The method of claim 1 has certain effects:

An "outflow of liquid having a lower animal cell density than the cell culture," and

"no more than 5% of the animal cells in the culture form aggregates of at least 5 cells during the continuous perfusion culturing."

However, even if the examiner interprets the claims as such, they are nearly insolubly indefinite. Applicant must clarify by claim amendment whether steps (a)-(c) are the only required steps and whether they are performed sequentially or simultaneously; that is, applicant should make clear by amendment whether the "circulating" is part of the "continuous perfusion culturing" or a subsequent step. Applicant must clarify by amendment whether the "alternating tangential flow" refers to the circulation, the filter module itself, the fibers of the module, the perfusion culturing, or some other element. Applicant must make clear by amendment whether the "continuous perfusion culturing"

in which aggregates are limited is the entire method or merely one element (i.e., whether aggregates may form during the "circulating"). Applicant must clarify by amendment whether medium flows "over" the filter module (i.e., on top of it) or "through" it, as suggested by the specification's definition at page 2, lines 14-17. Applicant must clarify by amendment whether "lower animal cell density" refers to the number of cells per volume of medium or to cells that are physically lower in density than other cells (e.g., adipocytes float on water, while lipid droplet-free cells do not).

Claim 1 refers to "alternating tangential flow," which the examiner queries because it appears to refer to a product made by Refine Technology Co. See Voisard et al., *Biotechnology and Bioengineering* 82: 751-65 (on 11/13/07 IDS) at 752, column 2. Applicants should clarify whether "alternating tangential flow" is a trade name for Refine Technology Co.'s apparatus or whether the person of ordinary skill in the art would understand the full scope of this term. If the latter is the case, applicants must support their assertion with at least one piece of patent or non-patent literature that employs the phrase in a manner other than in reference to Refine Technology Co.'s apparatus. If "alternating tangential flow" is indeed a trade name, applicants must amend the claim such that it recites generic language. The Office will not participate in the devaluation of trademarks. Clarification is required.

Clarification of all of these points is required. Because claims 2-9 and 11-15 depend from indefinite claim 1 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 2 refers to "Formula 1," which is confusing because there is no formula clearly annotated as Formula 1. It is not clear how, if at all, the reference to "Formula 1" clarifies the scope of the claim, since the claim recites a formula. Clarification is required.

Claim 2 refers to "cell culture volume" and also "viable cells per unit of volume," but it is not clear whether the "volume" in the latter expression is the "cell culture volume," the volume of the culturing vessel (which could contain some air space), or some other volume. Furthermore, the culture "comprises" animal cells, so other cells may be present; therefore, applicants must clarify whether the "viable cells" in the final line of claim 2 are necessarily the "animal cells" of the culture or whether they include all viable cells from any source. Clarification is required.

Claim 2 includes a formula for "perfusion rate," which is expressed in "liters per day." The formula refers to "specific perfusion rate," which is defined at page 4, lines 33-35, as "the rate in which the cell culture medium is fed to the cell culture expressed as the volume of medium added per viable cell per time unit." It is not clear whether the specific perfusion rate is truly "the volume of medium added per viable cell per time unit" or, rather, "[the volume of medium added per viable cell] per time unit." It is not clear whether the time unit is in the numerator or denominator of this fraction; the rules of mathematics would seem to require the latter. Clarification is required.

Most importantly, however, claim 2 appears to add nothing to the scope of claim 1. Claim 2 does not set forth any limit on the permissible and excluded perfusion rates.

Applicant should clarify how claim 2, on its own without reference to claim 3, limits claim 1.

Claim 3 refers to "animal cells" per day, but the definition of specific perfusion rate in the specification is not so limiting. Clarification is required.

Claim 4 requires "additional cell culture medium" be added to the culture, but it is not clear whether this is in addition to the cell culture "added" in claim 1 or whether it is merely a reference to the addition in claim 1. Clarification is required.

Claim 5 refers to a "steady state" reached by the cells, but it is not clear whether this limitation refers to their division or to some other state. Clarification is required.

Claim 6 recites, "wherein a volume of biomass is removed **of** between 2 and 40% of the total volume of the cell culture per day," which is confusing because it does not clearly conform to the rules of standard English. Clarification is required.

Claim 7 requires that the alternating tangential flow "is achieved using [pumps]," which is confusing because the word "using" does not particularly describe the nature of the "use." It is not clear what active steps are actually carried out with these pumps. Clarification is required.

Claims 8 and 9, like claim 1, recite end results of a method without making clear whether it is the inherent effect of the method steps in claim 1 and only those steps, or whether it is achieved only by carrying out additional steps or under certain conditions. Clarification is required.

Claim 15 requires that the biological substance produced by the cells in claim 13 is "further purified in downstream processing," but it is not clear whether this claim is

intended to add further active steps in which the substance is purified in a laboratory or whether it is merely describing the action of the cells on the substance (e.g., the "biological substance" may be ATP, which is synthesized in mammalian cells and "purified" as it moves out of the mitochondria and into the cytoplasm). Clarification is required. If the claim is intended to recite an active step, it must positively recite an active step.

Claim Rejections - 35 USC § 103

The language of a claim must make it clear what subject matter the claim encompasses to adequately delineate its "metes and bounds." See, e.g., *In re Hammack*, 427 F 2d. 1378, 1382, 166 USPQ 204, 208 (CCPA 1970). The courts have also indicated that before claimed subject matter can properly be compared to the prior art, it is essential to know what the claims do in fact cover. See, e.g., *In re Steele*, 305 F 2d. 859, 134 USPQ 292 (CCPA 1962). In this case, the claims are nearly so indefinite as to preclude a substantive search by the examiner. However, In the interest of compact prosecution, the examiner has made an earnest effort to examine applicants' invention as defined by the claims. The fact that the examiner has attempted to interpret the claims for art rejection purposes does not obviate applicants' obligation to particularly point out and to distinctly claim the invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyung et al. (1994, *Cytotechnology* 14: 183-90; reference 8 on 7/23/10 IDS) taken in view of Shevitz (2003, U.S. Patent 6,544,424; on 11/13/07 IDS), and Furey (2000, *Genetic Engineering News* 20: 52-53; on 11/13/07 IDS).

Claim 1 is interpreted as being drawn to a method comprising (a) carrying out continuous perfusion culture of animal cells in culture medium, (b) adding culture medium to the culture, and (c) circulating the animal cells in culture medium over a filter module that comprises hollow fibers "in an alternating tangential flow" until the culture contains at least 80 x 10^6 cells per mL of medium. Steps (a), (b), and (c) may be carried out simultaneously or sequentially. In the method of claim 1, a liquid is removed in some manner, an "outflow," that contains fewer cells than the remainder of the culture. In claims 2 and 3, the medium is added at some rate. In claims 4-6, "biomass" (i.e., any composition containing some product of the cells) is removed from the culture system. In claim 7, two pumps are employed. Claims 8 and 9 attempt to describe effects of the

method. Claims 11 and 12 limit the source of the cells. Claims 13-15 require that the cells produce some substance, i.e. any protein, that can be purified to any degree using any means.

Kyung teaches culturing human embryonic kidney epithelial cells ("293 cells") in continuous perfusion culture in a bioreactor until the cells reach a density of approximately $100x10^6$ cells/mL. Page 184 under "Cell culture"; Figure 2. Kyung's bioreactor employs two peristaltic pumps and five ports to remove spent media ("biomass") and to provide fresh media at a controlled rate. Pages 184-85, under "Bioreactor instrumentation." During the culturing, Kyung's 293 cells produce protein C. Figure 2. Kyung teaches optimizing the calcium concentration of the medium in order to reduce cell aggregates. Page 188, first full paragraph. Kyung's culturing method yields viability greater than 95%. Page 188, first full paragraph.

Kyung does not teach a bioreactor that provides alternating tangential flow. Kyung does not specifically point out the number or size of cell aggregates that result from the method.

Shevitz teaches a bioreactor comprising hollow fibers **18**, two pumps **24** and **46**, and a filter compartment **4** that provide an alternating tangential flow ("ATF") that continuously filters fluids by flowing the media first in one direction, then in another. Column 3, line 42, through column 4, line 11; Figure 1; columns 6-8. Shevitz's bioreactor permits the culture to achieve high cell concentrations and to reach a steady state. Column 3, lines 18-28; column 14, lines 44-47. Shevitz's bioreactor eliminates large cell aggregates from the culture in two ways: by preventing their formation with the

two-way flow (column 3, lines 37-41; column 9, lines 64-66; column 15, lines 7-12) and by filtering out the ones that do form (column 14, line 64, through column 15, line 7).

Furey teaches culturing cells in Shevitz's ATF bioreactor. Figure 3; page 53, under "ATF system." Furey teaches that cells so cultured grow and produce proteins. Figure 3, triangle and diamond symbols. Furey teaches that the ATF bioreactor can be perfused at a steady rate. Figure 3, "x" symbols.

A person of ordinary skill in the art would have had a reasonable expectation of success in carrying out Kyung's 293 cell culturing in Shevitz's ATF bioreactor because both Kyung's and Shevitz's bioreactors permit long term, continuous perfusion culture. Furthermore, Shevitz specifically contemplated culturing cells in the bioreactor, and Furey demonstrated that the ATF bioreactor can support mammalian cell culture. The skilled artisan would have been motivated to substitute Shevitz's ATF bioreactor for Kyung's because Shevitz's bioreactor prevents the formation of cell aggregates, which Kyung recognized as being undesirable in suspension culture of mammalian cells.

The skilled artisan would have had a further reasonable expectation of confining cell aggregates to less than 5% of the total culture and fewer than five cells per aggregate because Kyung teaches that aggregate formation may be controlled by optimizing the contents of the culture medium and Shevitz's ATF bioreactor is specifically designed to eliminate aggregates and to inhibit their formation. The skilled artisan would have been motivated to eliminate aggregates because Kyung recognized that they are undesirable in mammalian cell suspension culture.

The selection of the rate of addition of fresh medium and the amount of spent medium to remove would have constituted routine optimization at the time of the invention, the skilled artisan recognizing Kyung's teaching that the amounts fed and withdrawn may be modulated by changing the pump settings and Shevitz's inclusion of numerous controls that optimize culture conditions (e.g., the valves **10**, **19**, **21**, and **23** see column 6, lines 64-66, e.g.; a controller, see column 8, lines 27-32; see also claim 27, e.g.).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute Shevitz's ATF bioreactor for Kyung's in order to facilitate long-term perfusion culture; to prevent aggregate formation; and to control the addition and removal of medium, especially given Furey's working example in which mammalian cells were successfully cultured in Shevitz's ATF bioreactor.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action in order to assist the examiner with double patenting analysis in the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651